II.C.2.

- Three CTR studies research the neurochemical mechanisms of nicotine withdrawal;[573]

Andersson K, Fuxe K, Eneroth P, *et al.*, Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine, nerve terminal systems . and on the secretion of pituitary hormones in the male, *Naunyn Schmiedebergs Arch Pharmacol* 1989;339(4):387-396.

Cronan T, Conrad J, Bryson R, Effects of chronically administered nicotine and saline on motor activity in rats, *Pharmacol Biochem Behav* 1985;22(5):897-899.

Domino EF, Lutz MP, Tolerance to the effects of daily nicotine on rat bar pressing behavior for water reinforcement, *Pharmacol Biochem Behav* 1973; 1(4):445-448.

Fuxe K, Andersson K, Eneroth P, *et al.*, Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987;225-262.

Lapin EP, Maker HS, Sershen H, *et al.*, Dopamine-like action of nicotine: lack of tolerance and reverse tolerance, *Brain Res* 1987;407(2):351-363.

Nelsen JM, Goldstein L, Improvement of performance on an attention task with chronic nicotine treatment in rats, *Psychopharmacologia* 1972;26(4):347-360.

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:125-139.

Stitzer M, Morrison J, Domino EF, Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists, *J Pharmacol Exp Ther* 1970;171(2):166-177.

Wenzel DG, Azmeh N, Clark IJ, Studies on the acute and chronic depressor actions of nicotine in the rat, *Arch Int Pharmacodyn Ther* 1971;193(1):23-36.

Westfall TC, Brase DA, Studies on the mechanism of tolerance to nicotine-induced elevations of urinary catecholamines, *Biochem Pharmacol* 1971;20(7):1627-1635.

[573] Andersson K, Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catechalamine nerve terminal systems and the secretion of pituitary hormones in the male, *Naunyn Schmiedebergs Arch Pharmacol* 1989;339(4):387-396.

Fuxe K, Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain, in *Tobacco Smoking and Nicotine: A Neurobiological Approach,* eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:225-262.

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach,* eds, Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987;125-139.

- Two CTR studies investigate the effects of nicotine withdrawal on performance;[574]
- Two CTR studies show that nicotine is psychoactive and produces clearly discriminable stimulus effects;[575] and
- Two CTR studies show that nicotine can enhance the rewarding effects of electrical brain stimulation.[576]

Indeed, seven CTR studies state expressly that nicotine is an addictive or dependence-producing drug.[577] For instance, one CTR-funded study stated that "*smoking*

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[574] Heimstra NW, Fallesen JJ, Kinsley SA, *et al.*, The effects of deprivation of cigarette smoking on psychomotor performance, *Ergonomics* 1980;23(11):1047-1055.

Heimstra NW, Bancroft NR, DeKock AR, Effects of smoking upon sustained performance in a simulated driving task, in the effects of nicotine and smoking on the central nervous system, *Ann NY Acad Sci* 1967;142:295-307.

[575] Chance WT, Kallman MD, Rosecrans JA, *et al.*, A comparison of nicotine and structurally related compounds as discriminative stimuli, *Br J Pharmacol* 1978;63(4):609-616.

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300.

[576] Olds ME, Domino EF, Comparison of muscarinic and nicotinic cholinergic agonists on self-stimulation behavior, *J Pharmacol Exp Ther* 1969;166(2):189-204.

Pradhan SN, Bowling C, Effects of nicotine on self-stimulation in rats, *J Pharmacol Exp Ther* 1971;176(1):229-243.

Deneau GA, Inoki R, Nicotine self-administration in monkeys, in The effects of nicotine and smoking on the central nervous system, *Ann N Y Acad Sci* 1967;142:277-279.

Other research jointly funded by the tobacco industry examines nicotine's ability to serve as a positive reinforcer in self-administration studies involving monkeys. *See* 60 FR 41642.

[577] Bosse R Gamery AJ, Glynn RJ, Age and addiction to smoking, *Addict Behav* 1980;5(4):341-351.

Martin WR, Van Loo GR, Iwamoto ET, *et al.*, *Tobacco Smoking and Nicotine: A Neurobiological Approach* (New York: Plenum Press, 1987).

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach,* eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:125-139.

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300.

is a form of dependence no less binding than that of other addictive drugs."[578] Similarly, another CTR-funded study observed that "*compelling evidence now exists that regular smoking is a form of drug addiction to nicotine.*"[579]

The Agency received no comments disputing FDA's characterization in the Jurisdictional Analysis of any of these CTR-funded studies. Thus, these uncontested studies demonstrate that the entire cigarette industry had detailed knowledge of the pharmacological effects of nicotine on the brain, including knowledge of research funded by the industry that found nicotine to be an addictive drug.

Collectively, these CTR studies and the studies conducted by individual cigarette manufacturers show that the cigarette manufacturers have acted like traditional pharmaceutical companies. Before marketing a prescription drug, a pharmaceutical company studies the pharmacokinetics of the drug (how it is absorbed into the body, metabolized, and excreted), the pharmacodynamics of the drug (what specific effects the drug has on the body's chemistry and metabolism as it makes its way through the body), and the clinical effects of the drug (whether the drug is effective in producing the desired

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Svensson TH, Grenhoff J, Engberg G, Effect of nicotine on dynamic function of brain catecholamine neurons, in *The Biology of Nicotine Dependence,* eds. Bock G, Marsh J, *CIBA Foundation Symposium* 1990;152:169-180.

Tung CS, Ugedo L, Grenhoff J, *et al.,* Peripheral induction burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids, *Synapse* 1989;4(4):313-318.

Williams JS, Crumpacker DW, Krier MJ, Stability of a factor-analytic description of smoking behavior, *Drug Alcohol Depend* 1980;5(6):467-478.

[578] Bosse R Gamery AJ, Glynn RJ, Age and addiction to smoking, *Addict Behav* 1980;5(4):341-351 (emphasis added).

[579] Svensson TH, Grenhoff J, Engberg G, Effect of nicotine on dynamic function of brain catecholamine neurons, in The *Biology of Nicotine Dependence,* eds. Bock G, Marsh J, *CIBA Foundation Symposium* 1990;152:169-180 (emphasis added).

therapeutic or physiological effects). The cigarette manufacturers have conducted or funded the same studies for nicotine. As a result, the cigarette manufacturers' understanding of the pharmacological effects and uses of nicotine are closely analogous to—if not more extensive and sophisticated than—the understanding any pharmaceutical company has of traditional drug products.

e. Three Decades of Statements and Research by Cigarette Manufacturers Are Sufficient to Establish Intent

As discussed in section II.C.1., above, the statements and research of a manufacturer are relevant evidence of the uses of a product that are "intended" by the manufacturer. This evidence shows that when the manufacturers offer cigarettes for sale, they "have in mind" that their products will be purchased for specific pharmacological uses by consumers. Hence, the evidence is sufficient to establish that the effects of cigarettes on the structure and function of the body are "intended" by the manufacturers.

The cigarette manufacturers assert, however, that the statements and research relied upon by the Agency are not reliable evidence of the cigarette manufacturers' intent in this case. Among other things, they argue that the three decades of tobacco company statements and research on the addictive and other pharmacological effects of nicotine contained in the administrative record are irrelevant to the intended use of cigarettes and smokeless tobacco because the statements were made and the research was conducted over a period of many years and are not contemporaneous with the sale of currently marketed products.[580]

[580] Other arguments of the manufacturers concerning the evidence that may be used to establish intended use are addressed in section II.E., below.

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FDA disagrees. The extensiveness of the statements and research of the cigarette manufacturers in the administrative record, most of which have only recently become available, reflects a remarkably consistent pattern of the industry's views, repeated frequently over time. These documents and statements establish the knowledge and belief of tobacco company officials that cigarettes have, and are predominantly used by consumers for, pharmacological effects. The fact that these statements span three decades simply demonstrates that the companies' knowledge and beliefs about the pharmacological effects and uses of cigarettes are both long-standing and consistent. As described in section II.A.5., above, commercial cigarettes marketed today contain a level of nicotine that is sufficient to produce addiction and other pharmacological effects. Thus, statements made 30 years ago about the pharmacological effects of nicotine in cigarettes are equally relevant to the cigarettes being marketed today. Moreover, as discussed above, many of the statements and research relied upon by FDA are of recent origin.

Tobacco industry comments also argue that statements of individuals employed, or formerly employed, by the manufacturers are not relevant to establishing the intent of any manufacturer because they are not formal statements of company policy. According to one manufacturer's comments, the only statements that are evidence of the manufacturer's "institutional intent" are those that have been adopted by the manufacturer "after whatever formalities required by the decision-making procedures of the institution have been followed."[581]

[581] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 24. *See* AR (Vol. 519 Ref. 103).

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FDA disagrees that the statements of tobacco industry employees are not evidence of the intended use of the product. FDA is relying on the statements as evidence that the tobacco companies know that nicotine in tobacco has pharmacological effects and that consumers use tobacco to obtain those effects. Many of the statements come from executives at the companies. As one court observed, in a case relied upon by a tobacco company comment:

> When a major company executive speaks, "everybody listens" in the corporate hierarchy, and when an executive's comments prove to be disadvantageous to a company's subsequent litigation posture, it cannot compartmentalize this executive as if he had nothing more to do with company policy than the janitor or watchman.

Ezold v. Wolf, 983 F.2d 509, 546 (3d Cir. 1992) (internal citation omitted).

Moreover, many of the statements relied upon by FDA come from individuals whose function within the company was to research and understand the motives for smoking and who regularly communicated those views to company management. A corporation ordinarily relies on its research department to answer scientific questions, such as the pharmacologic effects of its product on users and the purposes for which consumers use the product. The statements quoted by FDA show a highly consistent pattern of views within and among the research departments of the cigarette companies, demonstrating that the statements are not the idiosyncratic opinions of a few individuals within one company, but widely shared views.

Indeed, the record shows that the cigarette manufacturers did in fact rely upon and regularly consult with their research scientists. In the case of Philip Morris, for instance, the CEO of Philip Morris, the president of Philip Morris USA, and vice presidents and directors from functions such as marketing met on a monthly basis with senior officials and

scientists from the company's research and development department to discuss Philip Morris' basic and applied research and other topics.[582] These regular meetings, the occurrence of which Philip Morris does not dispute, show that the knowledge and views of the Philip Morris scientists were regularly sought by and communicated to the officers at the head of the company.

For these reasons, the statements and research of the cigarette manufacturers are sufficient evidence to establish that the manufacturers intend to affect the structure and function of the body. As FDA's regulations recognize, "objective intent" can be established by evidence that "a manufacturer knows, or has knowledge of, facts that would give him notice," that a product will be used for pharmacological purposes. 21 CFR 201.128, 801.4.[583]

3. The Cigarette Manufacturers Have Conducted Extensive Product Research and Development To Optimize the Delivery of Nicotine

The tobacco industry documents in the administrative record show not only that the cigarette manufacturers "have in mind" that cigarettes will be used for specific pharmacological purposes, but also that they have "designed" cigarettes to ensure that smokers receive a pharmacologically active dose of nicotine. The evidence in the record contains two categories of evidence of the manufacturers' design: (1) the evidence of the

[582] Declaration of Uydess IL (Feb. 29, 1996), at 22-23. *See* AR (Vol. 638 Ref. 1).

[583] The Freedom of Information Act (FOIA) and Title VII cases cited by the comments do not purport to set forth a standard for assessing objective intent under public health statutes like the Federal Food, Drug, and Cosmetic Act, and the two statutes serve different purposes than the Act. They are, therefore, not controlling here. The FDA regulation cited by the comments is similarly inapplicable to the question of what evidence is relevant to establishing intended use. FDA is not contending that the statements of a single tobacco company employee can bind the company in such a way that the totality of the remaining evidence of intent can be overridden. Here, however, there is a consistent pattern of internal statements that, taken as a whole, are highly relevant to intent.

manufacturers' extensive product research and development to identify the doses of nicotine needed to produce pharmacological effects and to optimize the delivery of nicotine to smokers, which is discussed below; and (2) the evidence of the manufacturers' control and manipulation of nicotine in marketed cigarettes, which is discussed in section II.C.4., below.

The product research and development efforts described in the administrative record indicate that for three decades the cigarette manufacturers have strived to develop ways to maintain pharmacologically active doses of nicotine despite consumer demands for "healthier," lower-yield products. A primary focus of the cigarette manufacturers' efforts has been to deliver sufficient nicotine to provide the desired pharmacological effects of nicotine while at the same responding to consumer health concerns by reducing tar deliveries. Industry documents disclose research to determine the dose of nicotine that must be delivered to ensure "pharmacological satisfaction,"[584] as well as estimates by company scientists of the range of acceptable nicotine doses to produce pharmacological effects. These documents show that the manufacturers are aware that consumers will not accept cigarettes that do not deliver a pharmacologically active dose of nicotine.

The manufacturers' product research and development efforts have involved a wide variety of approaches to ensure delivery of an adequate dose of nicotine, including changes in tobacco blends; chemical manipulation to liberate "free" nicotine; filter and ventilation designs that selectively remove more tar than nicotine; the development of high-technology nicotine delivery devices that provide smokers nicotine but virtually no

[584] BATCO Group R&D Research Programme, 1984: Proposed revisions for 1985-87, Research Conference, Southampton, England (Sep. 1984), at 2. *See* AR (Vol. 26 Ref. 369-1).

tar; genetic engineering of tobacco plants to enhance nicotine content; the search for nicotine "analogues" that retain nicotine's reinforcing abilities; and research into compounds that act synergistically to strengthen nicotine's pharmacological effects. As discussed in section II.C.4., below, many (but not all) of these methods are used in cigarettes currently marketed to the public.[585]

a. Philip Morris' Product Research and Development Efforts

Evidence on the research and development efforts of Philip Morris demonstrates that the company believes that cigarettes must deliver sufficient nicotine to produce pharmacological effects in smokers and that the company conducted extensive research to optimize nicotine delivery from its cigarettes.

In a 1972 document, Philip Morris senior scientist William Dunn discussed the basis for the company's concerns about lowering nicotine levels below a certain minimum. Dunn related consumers' lack of interest in cigarettes providing less than 1 mg of nicotine to the fact that 1 mg of nicotine "readily" produces the desired "physiological response":

> Despite many low nicotine brand entries into the marketplace, none of them have captured a substantial segment of the market. In fact, critics of the industry would do well to reflect upon the indifference of the consumer to the industry's efforts to sell low-delivery brands. 94% of the cigarettes sold in the U.S. deliver more than 1 mg of nicotine. 98.5% deliver more than 0.9 mg.[586] *The physiological response to nicotine can readily be elicited by cigarettes delivering in the range of 1 mg of nicotine.*[587]

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[585] The evidence discussed in section II.C.3. is also relevant to, and provides further support for, the Agency's finding that the cigarette manufacturers "have in mind" that their products will be used for pharmacological purposes.

[586] Dunn WL, *Motives and Incentives in Cigarette Smoking* (1972) (summary of CTR-sponsored conference in St. Martin), at 4. *See* AR (Vol. 12 Ref. 133).

[587] *Id.* (emphasis added).

A 1978 Philip Morris document shows a similar focus on identifying the minimum amount of nicotine necessary to produce pharmacological effects, referred to as the threshold level of nicotine in the body that satisfies consumers' "nicotine need."[588] The document discussed plans to study cigarettes in which the tar level was kept constant, but the nicotine level was varied. The purpose of the study was to determine how smokers react to levels of nicotine so close to the minimum that "the total nicotine in the [smoker's] system remains at or near the nicotine need threshold."[589]

This focus on producing cigarettes that provide pharmacologically active doses of nicotine is a prominent feature of Philip Morris' development of low-tar cigarettes. William Farone, the former director of applied research at Philip Morris, described the goals of Philip Morris' product research and development efforts in a statement submitted to the Agency. According to Farone, "*a key objective of the cigarette industry over the last 20-30 years*" was decreasing tar while maintaining the delivery of nicotine, and that tobacco company researchers therefore considered it a "top priority" to "[m]inimiz[e] the exposure to the potential negative health effects of the undesirable chemical components in tar *while maintaining an acceptable and pharmacologically active nicotine level.*"[590] This involved extensive product research and development. Farone stated:

> Extensive, in some instances ground breaking, research by the tobacco industry was necessary to construct a cigarette that ensured an adequate delivery of nicotine as the cigarette market evolved from the traditional full flavored, unfiltered product of the

[588] Dunn WL, *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7670 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[589] *Id.*

[590] Farone WA, *The Manipulation and Control of Nicotine and Tar in the Design and Manufacture of Cigarettes: A Scientific Perspective* (Mar. 8, 1996), at 4 (emphasis added). *See* AR (Vol. 638 Ref. 2).